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US ARMY MEDICAL RESEARCH LABORATORY

FORT KNOX, KENTUCKY

REPORT NO. 554

THE SYNERGISM OF AUTONOMIC DRUGS ON OPIATE OR OPIOID-INDUCED ANALGESIA: A DISCUSSION OF ITS POTENTIAL UTILITY AND AN ANNOTATED BIBLIOGRAPHY

Capt Wayne O. Evans, MSC

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Report Submitted 29 August 1962

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REPORT NO. 554

THE SYNERGISM OF AUTONOMIC DRUGS ON OPIATE OR OPIOID-INDUCED ANALGESIA: A DISCUSSION OF ITS POTENTIAL UTILITY AND AN ANNOTATED BIBLIOGRAPHY

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10 October 1962

Pharmacology of the Combat Soldier
Task 04
Internal Medicine
USAMRL Project No. 6X60-01-001

Report No. 554
USAMRL Project No. 6X60-01-001-04

ABSTRACT

THE SYNERGISM OF AUTONOMIC DRUGS ON OPIATE OR OPIOID-INDUCED ANALGESIA: A DISCUSSION OF ITS POTENTIAL UTILITY AND AN ANNOTATED BIBLIOGRAPHY

OBJECT

The object of this paper is to gather together information pertaining to the potentiation of opiate-induced analgesia by autonomically active drugs to facilitate theoretical explanations of their action and considerations of the practical uses of this type of mixture.

RESULTS

The evidence indicates that combining an opiate with any one of a diverse group of autonomic drugs will result in an increase in the degree of induced analgesia. D-amphetamine was particularly considered since its addition to an opiate increases the analgetic effect by 60 to 100%. At the same time, d-amphetamine helps minimize the undesirable side effects of opiates by reducing the degree of nausea, constipation, sedation and mental depression; and by normalizing blood pressure, oxygen consumption, and respiratory rate.

CONCLUSION

The combination of d-amphetamine with an opiate for the induction of analgesia should offer certain unique advantages for use in civil disasters, combat military medicine, and in other similar situations in which environmental exposure, hemorrhage, and fear contribute to a danger of death due to shock. Its use would also include situations in which sedation is contraindicated due to a need to keep the patient ambulatory and cooperative.

RECOMMENDATION

The possibility of combat military use of this mixture should be given serious consideration. Studies should be conducted to provide an explanation for the potentiation effect and to seek further evidence of its practical applicability.

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THE SYNERGISM OF AUTONOMIC DRUGS ON OPIATE OR OPIOID-INDUCED ANALGESIA: A DISCUSSION OF ITS POTENTIAL UTILITY AND AN ANNOTATED BIBLIOGRAPHY

I. INTRODUCTION

Two major considerations have tended to restrict the utility of opiate and opioid alkaloids as analgesic agents: first, their tendency to produce tolerance and addiction; and second, the problems introduced by their side effects of respiratory depression, reduced blood pressure, mental depression, constipation, nausea, and sedation.

The problem of tolerance and addiction has not too greatly affected combat military usage since, generally, a trauma case receives opiates for a comparatively short period of time. However, the side effects produced by the actions of opiates on the autonomic nervous system do constitute a problem, especially in those situations in which shock is present or imminent. Shock is a very common danger when injury occurs under exposed environmental conditions, and the side effects of the opiates are such as to intensify shock, or to increase the likelihood of the appearance of profound shock (1, 2).

Considering these difficulties inherent in the use of opiates, a method of increasing their analgetic activity while reducing their depressant and shock enhancing effects would be of great use in situations in which shock, ability to carry out instructions, or the necessity of maintaining consciousness, contraindicates the use of an opiate alone as an analgesic.

II. DISCUSSION

A rather diverse group of autonomically active agents have been shown to potentiate the analgetic activity of opiates. The majority of the investigations relating to this effect are reported in the accompanying annotated bibliography. Evidence for potentiation has been put forth for parasympathomimetic agents such as neostigmine (3) and physostigmine (4), parasympatholytic drugs such as atropine and scopolamine (5), sympathomimetic agents such as d-amphetamine (6) and methamphetamine (7), sympatholytic drugs like chloropromazine (8) and dibenzyline (9), and drugs of the tryptamine and tryptophane type (10). Furthermore, there is no evidence of a relationship between the particular physiological changes usually considered in connection with

these drugs and the degree to which they are able to potentiate opiates (11).

At the present time we have no adequate theoretical explanation of this potentiation. Investigators have suggested three theories of action: 1) that an excitation of the central sympathetic nervous system produces analgesia and that the morphine effect is due to a release of adrenaline which facilitates sympathetic action (12), 2) that, since opiates act as cholinesterase inhibitors and morphine is potentiated by cholinesterase inhibitors, the induced analgesia is a "cholinergic" event (13); and 3) that, since all of the agents which potentiate morphine can be structurally related to the hypothesized central adrenergic "alpha" and "beta" receptors, the action of potentiation is through an active competition with morphine for adrenergic sites, thus leaving more opiate available for analgetic action (9). At present, the evidence available discounts the first two theories (5, 11, 14, 10) and not enough evidence exists to support the "adrenergic competition" hypothesis. However, regardless of the present lack of a theoretical explanation of this potentiation, empirical evidence does demonstrate the fact of its existence and its potential usefulness in combat military medicine or situations of civil disaster.

Of the various drugs which will potentiate an opiate-induced analgesia, d-amphetamine seems to offer the greatest practical utility because it counteracts the shock-enhancing aspects of morphine action. Also, more evidence exists as to its clinical effects when combined with opiates than for the other agents. The first mention of a true potentiation of an opiate-induced analgesia by d-amphetamine was presented by Ivy and his colleagues in 1944 (6, 15, 16). However, as early as 1941, Abreu and Handley (17) had shown that amphetamine could normalize respiratory depression and oxygen consumption in morphinized rats. Similarly, in 1941, DeVoine Guyot (18) reported that patients with coronary occlusion when treated with 0.5 gr to 0.75 gr of morphine alone would show more vomiting, inhibition of bowel action, respiratory depression, hypotension, and mental depression than when the same dose of morphine was given in combination with 10.0 mg of r-amphetamine. Also, Morrison and Abreu (19) showed that the depression of oxygen uptake in dogs by 10 mg/kg of morphine could be combated by 0.5 mg/kg of l-amphetamine, d-amphetamine, or r-amphetamine. In this study the d-amphetamine raised the depressed oxygen consumption by 22% and was superior to the racemic or levo-rotary forms.

In 1944, Ivy and his colleagues demonstrated that d-amphetamine could increase an opiate-induced analgesia in dogs (15), in mice (16),

and in man (6). In man, 16 mg of morphine sulfate in combination with 20 mg of d-amphetamine sulfate produced a degree of analgesia 60% greater than with the same dose of morphine alone. At the same time, the mixture overcame the depression of morphine on respiration and blood pressure, reduced nausea and vomiting, and normalized the critical flicker fusion threshold and choice reaction time of the subjects.

Between 1944 and 1950 the potentiation of opiate and analgesia by d-amphetamine was confirmed by Nickerson and Goodman (20) with normal subjects given isonipecaine. Also, Abel and Harris (21) showed the effect with obstetrical patients. During the same period, Handley and his colleagues (22, 23) reconfirmed the normalizing effects of amphetamine on respiration, pulse rate, and blood pressure of morphinized patients. They also showed that d-amphetamine was superior to metrazol, ephedrine, caffeine, and nikethamide in combating opiate side effects. Nickerson (24) in 1950 by testing the reduction of pain induced by immersion of the hand in ice water showed the opiate potentiating effect of d-amphetamine in humans by combining meperidine (100 mg) and d-amphetamine (10 mg).

The first large scale clinical test of an opiate mixed with d-amphetamine was conducted in 1951 (25). Abel and his associates demonstrated with 7,000 obstetrical cases that adding 5 mg of d-amphetamine to 10 mg of morphine would provide good analgesia with the minimum of side effects and also shorten the length of time to the first inspiration by newborn infant as compared to the time of inspiration of the infant for patients given morphine alone.

Since 1951 only a few investigators have shown interest in this problem area. Saxena and Gupta (26), Guseva (27), Matsumura et al (28), Witkin et al (29), and Evans (9, 30), have reconfirmed in laboratory studies the potentiation actions of amphetamine on opiate analgesia and sought theoretical explanations for the effect, but clinical interest seems to have waned.

Perhaps the explanation of the decline of clinical interest lies in the fact that in a modern hospital shock does not present the major problem that it once did. Thus, there is no pressing requirement for a morphine compound with little or no shock enhancing property even if it allows a reduction in the amount of opiate needed to obtain a satisfactory level of analgesia. Similarly, the overcoming of the mental depression and sedation produced by morphine has little advantage in the modern hospital.

On the other hand, the use of morphine in a civil disaster or in the combat military situation may be quite different in terms of the requirements placed upon the drug. The administration of 15 mg morphine from a pre-packaged syringe to a wounded man in a wet, muddy foxhole during a Korean winter presents problems not present in a hospital in the United States. In combat or in situations of civil disaster, every condition is present to maximize the possibility of death due to shock. It is in situations of this nature that the full potential of the mixture of an opiate with d-amphetamine would be realized.

III. CONCLUSION

It has been demonstrated in dogs, rats, mice, healthy humans, and patients that the addition of d-amphetamine to an opiate will increase its analgetic potency from 60 to 100%. At the same time the addition of d-amphetamine helps normalize the opiate side effects of respiratory depression, lowered oxygen consumption, hypotension, mental depression, constipation, and emesis.

It would seem that this combination could be of great use as a combat military analgesic and its potential should be further studied.

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AN ANNOTATED BIBLIOGRAPHY OF THE SYNERGISM OF ANALGESIA OF OPIATES BY AUTONOMIC DRUGS

ABEL, S., ZELDA B. BALL and S. C. HARRIS
The advantages to mother and infant of amphetamine in obstetrical analgesia. Amer. J. Obst. and Gynecol. 62: 15-27, 1951.

A clinical study of 7,000 cases given 1/6 gr of morphine alone or with 5 mg of d-amphetamine. Also 100 mg of demerol alone and with 1/150 gr of scopolamine. Clinical estimates of morphine-amphetamine on degree of analgesia were favorable. The first inspiration of infant was significantly retarded by morphine alone and normalized by the morphine-amphetamine mixture.

ABEL, S. and S. C. HARRIS
Morphine-benzedrine analgesic in obstetrics. (Abstract) Paper at Amer. Physiol. Soc. Proceedings, p. 67, 1947.

Nine patients were given 1/4 gr of morphine plus 5 mg of benzedrine for labor pain. First inspiration of infants born one to seven hours after drug was 42 sec mean (0-97). Good analgesia during labor was obtained as well as reducing the time to first inspiration by the infant.

ANGIBEAUD, P., L. BUCHEL and J. LEVY
Sur quelques phénomenés de synergie. I. Associations d'analgésiques et d'un spasmolytique considéré comme leur analogue structural. C. R. Soc. Biol. (Paris), 149: 258-261, 1955.

Using mice with a method of thermal and mechanical stimulation, the analgetic action of l-amidone, pethidine and morphine was measured alone and in combination with 2-(1-piperidyl) ethyl ester hydrocholoride of cyclohexylcyclohexanecarboxylic acid. Synergism was shown with l-amidone, but little effect with pethidine and none with morphine.

ABREU, B. E. and C. A. HANDLEY
The effects of benzedrine on respiration and oxygen consumption after morphine in men and rats. U. Calif. Pub. Pharmacol. 2: 99-104, 1942.

Six healthy men received 0.3 mg/kg morphine SO_4 orally. They were measured one hour later for: O_2 consumption, respiration, cardiac rate, pain by force of a dull point into hand. Also, O_2 from rats after 20 mg/kg morphine + 10 mg/kg of benzedrine. 0.3 mg/kg benzedrine used in humans.

0.3 mg/kg of morphine did not significantly depress O_2 consumption in humans nor could benzedrine be shown to have any effect to antagonize. In rats, morphine depression and benzedrine antagonism were shown.

BOREUS, L. O. and F. SANDBERG

The influence of three phenothiazine derivatives and of amphenazole on the action of methadon. Studies with two algesimetric methods in untrained human subjects. J. Pharm. (London), 11: 449-455, 1959.

Chloropromazine and acepromazine showed some analgesic activity using heat to the thumb nail as a test. Mepazine had no activity. By this test chloropromazine and acepromazine did not potentiate methadone and mepazine antagonized its analgetic action. Amphenazole had no effect on methadone and a slight activity by itself.

BUCHEL, L., J. LÉVY and O. TANGUY

Sur la potentialisation de l'action analgesique de la l-methadone par la 5-hydroxytryptamine (sérotonine). C. R. Acad. Sci. 246: 2947-2949, 1958.

Serotonin enhances analgetic action of l-methadon using mechanical stimuli. Reserpine promoted release of serotonin but antagonized methadon.

CHANG TAN-MU, TAH-CHAO FONG and FU-HAN LUE

Potentiating effects of diphenhydramine on the analgesic action of Han-Fang-Chi and some other analgesics. Acta Physiol. Sinica, 21: 133-141, 1957.

Using the method of Reinhard et al the alkaloids of Stephania tetranda S. Moore (tetrandrine) and also morphine, pethidine and phenazone were shown to be analgetic alone. Diphenhydramine

significantly potentiated the analgetic action of all of these compounds.

CHEN, J. Y. P.

Analgesic-potentiating and diuretic effects of 1-dl-methylamino-3-phenyl-4-methyl-hexane HCl (z-4) and 1-dimethylamino-2-phenyl-3-methyl-pentane HCl (z-134). J. Pharmacol. exp. therap. 117: 451-460, 1956.

Used hot plate with mice and found a true potentiation of 7 mg/kg of morphine by: z-134, 20 mg/kg; z-4, 20 mg/kg; chloropromazine, 2 mg/kg. Similar results with demerol and tail pinching method. Drugs not analgetic at these doses by themselves. z-4 and z-134 were respiratory stimulants in pentobarbitalized dogs. Also, lowered intestinal tone. z-4 and z-134 increased urine output by 500% over saline controls. Both produce a transitory fall in blood pressure. No hypnotic potentiating effects with pentobarbital. Toxic dose of 93 mg in rat produces central excitement and convulsions.

CHRISTENSEN, E. M. and E. G. GROSS

A comparison of the analgesic effects on human subjects of 6 dimethylamino-4-4 diphenyl-3-heptanone (AN148), morphine and meperidine (demerol) and the relative efficiency of AN148 for preoperative and postoperative use. J. A. M. A. 137: 594-599, 1948.

Used Hardy, Wolff, and Goodell method with eleven trained human subjects. Subjects guessed compounds used sometimes. Gave either 0.3 mg of atropine or scopolamine with methadon (2.5 mg), morphine (10 mg) and meperidine (50 mg). In all cases period of analgesia was shortened and reduced threshold increases of analgesic. Neostigmine at a dose of 0.5 mg caused an increase in threshold by itself and also a synergism with opiates.

CHRISTIE, G., S. GERSHON, R. GRAY, F. H. SHAW, I. McCANCE and D. W. BRUCE

Treatment of certain side effects of morphine. Brit. Med. J. 5072: 675-680, 1958.

Normal humans given 20 mg or 30 mg of morphine alone or with amiphenazole or cyclizine. Both reduced vomiting, nausea or sleepiness of morphine. Amiphenazole at 40-100 mg particularly helpful. No respiratory depression.

COOK, L., GERALDINE NAVIS and E. J. FELLOWS
Enhancement of the action of certain analgetic drugs by β-diethylaminoethyldiphenylpropylacetate hydrochloride (SKF No. 525A). J. Pharmacol. exp. therap. 112: 473-479, 1954.

The investigators used tail flick method in rats and found a true potentiation at 100 mg/kg of SKF 525A of morphine; 2 mg of 4.6x, meperidine, 10 mg of 2.2x; also of demerol, 3 mg, methorphinan 0.3 mg and codeine 60 mg. Did not effect morphine induced depression of respiration. SKF 525A enhances analgetic response of morphine tolerant rats.

COURVOISIER, S., J. FOURNEL, R. DUCROT, M. KOLSKY and P. KOETSCHET
Propriétés pharmacodynamique du chlorhydrate de chloro-3 (dimethylamine-3-propyl)-10-phenothiazine (4560RP), étude experimentale d'un nouveau corp utilisé dans l'anesthésie potentialisée et dans l'hibernation artificielle. Arch. internat. pharmacodyn. 92: 305-561, 1953.

The investigators used the hot plate method with mice and found that chlorapromazine produced marked increases in analgetic potency and time of action of morphine, meperidine, aspirin, salicylamide, aminopyrine and phenacetin.

DE JONGH, D. K.
Remarks on the mechanism of analgesic action of morphine. Acta Physiol. Pharmacol. Neerl. 3: 164-172, 1954.

Using radiant heat stimulus in guinea pigs (method of Winder), tested morphine (4 mg/kg), salicylamide (50 mg/kg), prostigmine (0.025 mg/kg), atropine (1.0 mg/kg) alone and in combination. Each drug by itself raised the threshold. Morphine plus prostigmine was not even additive while atropine plus morphine was additive. Prostigmine and atropine were antagonistic. The results do not suggest that morphine acts through a cholinergic mechanism.

DE VOINE GUYOT, J.

The use of benzedrine sulfate to overcome the untoward effects of morphine in the treatment of coronary occlusion. J. Mo. St. Med. Assn. pp. 93-94, March 1941.

Human patients with coronary occlusion treated with 1/2 to 3/4 gr morphine plus 10 mg of benzedrine orally. Vomiting was controlled, bowel action inhibited far less, the blood pressure fall of 50 to 75 mm with morphine alone was reduced to 20 mm by combination. Mental depression was minimized.

EVANS, W. O.

The potentiation of opiate induced analgesia by stimulant drugs. I: The effect of monoamine oxidase inhibitors and caffeine. USAMRL Report No. 519, Ft Knox, Ky., 1961.

Using the jump-flinch method in rats codeine SO_4 was found at a dose of 30 mg/kg to be potentiated by about 65% by d-amphetamine (2.5 mg/kg) and antagonism by about 40% by caffeine citrate (12 mg/kg). Iproniazid (40 mg/kg), β-phenylisobutylhydrazine (5.0 mg/kg) and β-phenylisopropylhydrazine (5 mg/kg) were found to have no effect.

EVANS, W. O.

The potentiation of opiate induced analgesia by stimulant drugs. II: The effect of sympathomimetics. USAMRL Report, Ft Knox, Ky. (in preparation).

Using the jump-flinch method in rats 16 mg/kg of morphine SO_4 was found to be potentiated by 100% by both d-amphetamine (5 mg/kg) and methamphetamine (5 mg/kg). Morphine analgesia was also potentiated by about 60% by trimethylamine HCl (30 mg/kg). 3, 4-dihydroxybenzaldehyde (20 mg/kg) and 3, 4-dichlorobenzaldehyde (20 mg/kg). Isopropylamine (2 mg/kg), n-propylamine (2 mg/kg) and sec-butylamine (5 mg/kg) were found to antagonize morphine by about 50%. Pre-treatment with 30 mg/kg of phenoxybenzamine was found to potentiate morphine analgesia. The results suggest a relationship to alpha and beta adrenergic receptors, perhaps a competition of adrenergic agents and morphine.

FLODMARK, S. and T. WRAMNER

The analgetic action of morphine, esserine and prostigmine studied by a modified Hardy-Wolff-Goodell method. Acta Physiol. Scand. 9: 88-96, 1945.

Using 19 human subjects with radiant heat method to compare 15 mg of morphine with 3 mg of morphine plus 0.5 mg of prostigmine. Mixture was 40% more analgetic. Prostigmine at 1 mg and also esserine at 1 mg produced slight rises in threshold of pain.

GERSHON, S., D. W. BRUCE, N. ORCHARD and F. H. SHAW

Amipherazole and morphine in the production of analgesia. Brit. Med. J. 5092: 366-368, 1958.

500 cases treated with morphine and amiphenazole (2-4, diamino-5-phenylthiazole) (in doses up to 200 mg t.i.d.). Morphine may be given in large doses without risk. No sedation found, addiction to morphine doesn't develop with months of treatment. No euphoria is present with mixture. No withdrawal symptoms.

GOETZL, F. R., D. Y. BURRILL and A. C. IVY

The analgesic effect of morphine alone and in combination with dextroamphetamine. Proc. Soc. Exper. Biol. and Med. 55: 248-250, 1944.

Using mice with tail pinching method given 20 mg/kg of morphine SO_4 and 35 mg/kg of d-amphetamine. Mixture produced an increase in threshold to squeal of about 50% and eliminated the usual morphine induced Straub reaction. Action developed within 60 min to max and lasted six hours to base line return.

GOETZL, F. R., D. Y. BURRILL and A. C. IVY

The analgesic effects of sympathomimetics and the combination of morphine with amphetamine. Proc. Inst. Med. Chicago, 15: 87-88, 1944.

Using voltage to metal tooth filling in dogs and man. Used first twitch or first pain report. Found d-amphetamine enhanced analgesia. Results confirmed with tail pressure to squeal in mice.

GRIMMETT, M. R., K. D. NEAME and F. N. FASTIER

Interaction between 4-methyl-2 amino-pyridine (W45) and certain other drugs, particularly morphine. Proc. Univ. Otago. Med. Sch. 38: 9-10, 1960.

W45 has some analgetic potency of its own and also enhances that of morphine using pricking of a rat's ear as the method in doses 20-40 mg/kg of morphine and 2.0 to 6.0 of W45. Its own analgetic effects are not antagonized by nalorphine. Its own effect was increased by a pre-treatment with phenelzine but not effected by reserpine or amphetamine.

GRODEN, B. M.

Daptazole: an aid to morphine administration. Surgo,(Glasgow), 23: 122-125, 1957.

A review of the literature on the combination of amiphenazole and morphine. Concludes the combination is clinically useful.

GUSEVA, E. N.

Combined action of analgetic morphine substitutes with analeptics. Farmakol. I. Toksikol. 20: Suppl. 1, 1957 (Russian Text).

Morphine and morphine like drugs were combined with amphetamine (30 mg/kg), caffeine (0.3 mg/kg) or 5 (2-bromoallyl)-5-isopropylbarbituric acid (30 mg/kg). Mice were used to test analgetic potency. All potentiated morphine. Larger doses of caffeine or amphetamine antagonized morphine.

HANDLEY, C. A.

A comparison of the action of amphetamine with other central nervous system stimulants in morphine respiratory depression. Proc. and Trans. Texas Acad. Sci. 28: 95, 1945.

Same material as in Anesthesiology, 6: 561-564, 1945.

HANDLEY, C. A. and D. L. ENSBERG

A comparison of amphetamine sulfate with other stimulants of the central nervous system in morphine respiration depression. Anesthesiology, 6: 561-564, 1945.

Fourteen humans took 0.5 mg/kg s. c. of morphine SO_4. Five studied with each drug.

	Dose in mg/kg	Minute Vol. % increase over depressed state
Amphetamine SO_4	0.2	102
Caffeine and Na Benzoate	10.0	17
Ephedrine SO_4	0.5	30
Metrazol	5.0	21
Nikethamide	7.5	37

Amphetamine and ephedrine also raised morphine depressed pulse and blood pressure. None of the others did this.

HANDLEY, C. A., D. ENSBERG and H. M. SWEENEY

The relative efficiency of central nervous system stimulants in respiratory depression from morphine. Fed. Proc. 3: 75, 1944.

Eight human subjects given 0.5 mg/kg of morphine SO_4 produced consistent respiratory depression which was maximal after one hour. Stimulants were given one hour after morphine. 0.1 - 0.4 mg/kg of amphetamine (s.c.) increased respiration back to normal. Metrazol and caffeine produced a weak stimulation but not as effective as amphetamine.

HARRIS, S. C. and F. J. FRIEND

Contribution of adrenals to morphine analgesia. Fed. Proc. 6: 124, 1947.

Using tail pinching method in rats after 5 mg/kg of morphine SO_4 (s.c.). In rats with bilateral adrenalectomy, but with cortices autotransplanted to the anterior chamber of the eye, the effect of morphine was reduced by 40%.

HERZ, A.

Über die Potenzierung der Morphinwirkung durch Spasmolytica vom Typ des Scopolamis. Naunyn-Schmiedebergs Arch. Exp. Path. Pharmak. 238: 110-111, 1960.

The cataleptic-narcotic action of morphine is enhanced by scopolamine, benactyzine, trihexyphenydyl, caramiphen and beperiden. Muscle tone is greatly reduced. The analgetic actions of morphine are enhanced some by scopolamine. A large enhancement of analgesia occurs with phenglutarimide and beperiden. The active drugs are considered to be acting in a similar fashion to chloropromazine. Beperiden is 2 (Bicyclo [2:2:1] Hept-5-EN-2YL) phenyl-1-piperidenepropanol (it lowers Ach content of brain: see Haas, H. et al, Arch. Int. Pharmacodyn. 128: 204-252, 1960).

HURST, E. W. and O. L. DAVIS

Studies on the blood-brain barrier. III. Attempts to influence the passage of substances into the brain. Brit. J. Pharmacol. Chemotherap. 5: 147-164, 1950.

Using the reaction of rats to thermal stimuli the effect of a number of substances on morphine analgesia were studied by changes in mean reaction time. Of theocin, sodium lactate, hexamine, glycerol, adrenalin (.002 mg/100 g) + pituitrin and histamine (17.5 mg/100 g) only histamine and pituitrin + adrenaline changed morphine (0.2 mg/100 g) actions by potentiating analgesia. Also using various dyes it was found that neutral-red chloride (1 cc/100 g of 1%) given i.p. for four successive days prior to morphine produced a potentiation. No explanation was presented.

IVY, A. C., F. R. GOETZL and D. Y. BURRILL

Morphine-dextro-amphetamine analgesia. War Med. 6: 67-71, 1944.

21 healthy humans were given s. c. 16 mg of morphine SO_4 and and 20 mg dextroamphetamine. Recorded pain threshold by stimulating metal filling of tooth, critical flicker fusion, blood pressure, pulse rate and choice reaction time. D-amphetamine raised pain threshold of morphine about 60%. Mixture also raised CFF threshold above morphine, blood pressure, pulse rate were normalized and speeded choice RT. There was less nausea and vomiting following the mixture than with morphine alone. Drowsiness was much less with the mixture.

IVY, A. C., F. R. GOETZL, S. C. HARRIS and D. Y. BURRILL
The analgesic effect of intracarotid and intravenous injections of epinephrine in dogs and subcutaneous injections in man. Quart. Bull. Northwestern Univ. Med. Sch. 18: 298, 1944.

Using tooth pulp stimulation method in dogs they found that epinephrine, ephederine and amphetamine all produced a potentiation of morphine analgesia. These drugs also had some analgetic action of their own. Similar studies on man confirmed the results.

KNOLL, J. and E. KOMLOS
Die Analgetische Wirkung des Atropins und sein Synergismus mit Morphin und Prostigmin. Acta Physiol. Hung. 2: 57-68, 1951.

Used mice on hot plate method and found that at a dose of between 50-100 μg/kg atropine significantly potentiated the analgetic action of morphine at doses of 1-5 mg/kg. Similarly at a dose of 5 mg/kg scopolamine synergized the analgetic effects of morphine. Giving atropine plus prostigmine (0.1 mg/kg) plus morphine produced a degree of analgesia greater than any one or any combination of two of them.

KNOLL, J., E. KOMLOS and J. PORSZASZ
Analgesie und cholinesterasehemmung. Acta Physiol. (Budapest), 2: 478-491, 1951.

Used the mice on hot plate method to measure analgetic activity and cholinesterase activity of morphine, methadone, prostigmine, amidazophene, pethiadine and atropine. No relationship was found between ChE activity and analgesia. A synergism of analgetic activity was found between morphine and prostigmine. Used 5 mg/kg of morphine and 0.1 mg/kg of prostigmine.

KOMLOS, E., J. PORSZASZ and J. KNOLL
Morphin-Prostigmin Synergismus. Acta Physiol. Acad. Sci. (Hung), 1: 77-90, 1950.

Used hot plate method in mice and found prostigmine to potentiate morphine at doses 0.8 - 5.0 of morphine and 0.1 of prostigmine.

There was also a potentiation of toxicity. Atropine (320 mg/kg) reduced the synergism of toxicity.

KULSRESHTHA, J. K. and P. N. SAXENA
Effect of atropine and hyoscine on morphine induced analgesia. Indian J. Physiol. Pharmacol. 1: 204-207, 1957.

No significant changes in the AD_{50} of morphine in rats was produced in combination with 150-300 µg/kg or scopolamine HBr at 150 µg/kg at 300 µg/kg in rats scopolamine reduced analgesia.

MATSUMURA, M., S. TAKAORI and R. INOKI
Suppressive synergism of morphine with methamphetamine on the afferent pathways of the central nervous system in the cat. Jap. J. Pharmacol. 9: 67-74, 1959.

Cats under hexobarbital or spinal chord cut. Drugs given i.v. The effective dose of morphine was 6 mg/kg. Both morphine and methamphetamine suppressed cortical and intraspinal potentials of splanchnic afferent stimulation. Morphine was more potent at suppressing augmenting responses following repetitive stimulation of the medial leminicus. Definite synergism was shown for the drugs on this augmenting response. Methamphetamine more strongly suppressed recruiting responses following repetitive stimulation of nucleus centre median. Possibly some synergism here. Morphine inhibited cortical responses but methamphetamine did not. No synergism shown in the cortex.

McKENZIE, J. S.
The effect of amiphenazole on morphine induced analgesia in mice. Aust. J. Exp. Biol. Med. Sci. 38: 47-59, 1960.

Used hot plate method in mice and found amiphenazole to potentiate morphine analgesia by i.p., s.c., oral routes. Effects on codeine were mild and variable. Suggest use in clinic to reduce necessary amount of narcotic.

MERCIER, F. and PAULETTE ETZENSPERGER
Potentialisation par la spartéine de l'actavite analgesique experiméntale. C. R. Soc. Biol. 148: 1431-1434, 1954.

Used the D'Amour and Smith method with the rat. Both temperature and time to reaction were measured. Sparteine (10 mg/kg) was given with:

morphine 1.5 mg/kg	potentiate
morphine 2.5 mg/kg	"
diamorphine 0.5 mg/kg	"
codeine 20.0 mg/kg	"
dihydrocodeine 10.0 mg/kg	antagonize
dihydrocodethyline 10.0 mg/kg	no effect
dihydrone 1.0 mg/kg	"
piridosal 5.0 mg/kg	"
antipyrine 100.0 mg/kg	"
pyramiden 100.0 mg/kg	"
aspirine 60.0 mg/kg	potentiate
benzoxazolone 100.0 mg/kg	"

MERCIER, F. and PAULETTE MARINACCE

Influence exercée par un ester du diethylaminoéthanol sur l'activité expérimentale de quelques analgésiques centraux. C. R. Soc. Biol. 145: 1340-1342, 1951.

Using hot plate method of Woolfe and Macdonald animals received either morphine (2.5 - 5.0 mg/kg), dihydrone (2.0 mg/kg) or pethidine (10 mg/kg) alone or in combination with 25 mg/kg of an ester of diethylaminoethanol (anisylhydrocinnamol), an antispasmodic agent. The degree of enhancement of analgesia was the same as if the dose of morphine had been increased by 100%.

MERCIER, F., J. MERCIER, PAULETTE ETZENSPERGER and D. ROUILLON

Reinforcement par les ganglioplégiques des activités analgésiques et anesthésique locale expérimentale. C. R. Soc. Biol. 148: 1448-1450, 1954.

Used rats with the method of Lespagnol and Mercier in which the intensity of hot plate heat to reaction is measured. 1.5 mg/kg of morphine was enhanced by Sparteine (10 mg/kg), pendiomide (2.5 mg/kg), penthonium (2.5 mg/kg), hexamethonium (2.5 mg/kg) and tetraethylammonium (2.5 mg/kg). Enhancement up to 100% for Sparteine and down to 3% for tetraethylammonium. The analgetic activity was not prolonged.

MILOSEVIC, M. P.

The analgesic activity of sympathomimetic amines. Acta Med. Jugosl. 12: 111-119, 1958.

Contact heat in mice showed weak action of adrenalin which is blocked by adrenergic blockers. Adrenergic blockers potentiated methadone. Nalorphine did not block epinephrine effect. Amphetamine and methamphetamine potentiated opiate. Adrenaline does not potentiate opiate.

MORRISON, J. L. and B. E. ABREU

Effects of d-, l-, and r-amphetamine on oxygen consumption of morphinized dogs. Fed. Proc. 2: 88, 1943.

O_2 consumption in dogs given 10 mg/kg morphine SO_4 plus 0.5 mg/kg of r-amphetamine, d-amphetamine, or l-amphetamine. R-amphetamine raised O_2 consumption 13% above basal morphine level, d-amphetamine 22% and l-amphetamine 15%.

NICKERSON, M.

Analgesic effects of nitrous oxide and meperidine alone and combined with amphetamine. West. Soc. Clin. Rsch. p. 541, April 1950.

Used human subjects with ice water immersion method and dolorimeter with meperidine (100 mg oral) N_2O (33% by mask) with d-amphetamine (10-20 mg). Amphetamine potentiated the analgesia of meperidine, but not of N_2O. Very little change under any condition with dolorimeter but good results with ice water method.

NICKERSON, M. and L. S. GOODMAN

Synergistic isonipecaine-amphetamine analgesia. Fed. Proc. 6: 360-361, 1947.

Investigated human subjects with: cold water immersion, amperage applied to metal tooth filling and dolorimeter. 100 mg isonipecaine + 10 mg amphetamine orally affected as a potentiation only on the "deep pain" of ice water technique. Considered a factor of more "subjective factor" of deep pain.

PORSZASZ, J., J. KNOLL and E. KOMLOS

Wirkung der parasympathomimetika auf die analgesia. Acta Physiol. Acad. Sci. Hungaricae, 2: 469-477, 1951.

Used a modified hot plate method with mice. Found a synergism of morphine, methadone, amidazophen, dolantin and hexalgon by: prostigmine, 0.1 mg/kg; physostigmine, 0.1 mg/kg; carbachol, 0.25 mg/kg. Of these carbachol gave greatest degree of effect. Tetraethylpyrophosphate at dose of 0.5 mg/kg gave no synergism. Concluded that effect is not due to parasympathomimetic action.

SADOVE, M. S., M. J. LEVIN, R. F. ROSE, L. SCHWARTZ and F. W. WITT

Chloropromazine and narcotics in the management of pain of malignant lesions. J.A.M.A. pp. 626-628, June 1954.

Chloropromazine in dose of 25 mg orally b.i.d. was given to 30 patients while reducing their narcotic dose by 50%. All patients maintained a satisfactory degree of analgesia and some were better on the mixture than previously on narcotics alone. Similarly nausea and vomiting were reduced.

SAXENA, P. N.

Mechanism of cholinergic potentiation of morphine analgesia. Indian J. Med. Res. 46: 653-658, 1958.

The experimenter used albino rats with bulldog clamp on tail as analgesic measurement technique. Drugs given alone and in combination with morphine. Pilocarpine, DFP, prostigmine and atropine tested at doses from 50 to 200 μg/kg.

Drug	AD_{50} in mg/kg
morphine	3.36
morphine + pilocarpine	2.13* (significant)
morphine + 100 DFP	3.45
morphine + 100 prostigmine + 200 μg atropine	2.58

Thus atropine does not antagonize prostigmine potentiation of morphine. Also, DFP does not potentiate although it is a very strong anti ChE compound.

SAXENA, P. N. and G. P. GUPTA

Analgesia potentiating effects of ephedrine and methamphetamine. J. Indian Med. Prof. 4: 1553-1554 and 1599, 1957.

Analgetic level determined in rats by hot wire to tail method.

Drug	AD_{50} of morphine (mg/kg)
morphine	4.29
phenylbutazone	lethal at these doses
morphine + ephedrine (6.25 mg/kg)	2.94
morphine + ephedrine (12.50 mg/kg)	2.17
morphine + methamphetamine (1.2 mg/kg)	3.58
morphine + methamphetamine (2.5 mg/kg)	3.12

SCHAUMANN, W.

Zur hypothese eines cholinergen Wirkungsmechanismus des Morphins. Naunyn-Schmiedberg's Arch. Exp. Path. Pharmak. 237: 229-240, 1959.

Using the Haffner method in mice it was found that morphine analgesia was potentiated by neostigmine and physostigmine. ChE inhibition by morphine previously found in vitro could not be confirmed in vivo. Irreversible peripheral inhibition of ChE had no effect on morphine analgesia. Morphine potentiated the toxicity of neostigmine, but not of physostigmine in mice. A cholinergic mechanism of morphine seems unlikely.

SCHNEIDER, J. A.

Reserpine antagonism of morphine analgesia in mice. Proc. Soc. Exper. Biol. and Med. 87: 614-615, 1954.

Using tail flick method in mice given 10.0 mg/kg of morphine SO_4 alone and with either reserpine (10.0 mg/kg) or chloropromazine (10 mg/kg). Reserpine antagonized analgesia while chloropromazine slightly enhanced it and considerably prolonged it.

SCHNEIDER, J. A. and MARIE McARTHUR
Potentiation action of ibogaine (Bogadin TM) on morphine analgesia. Experimentia, 12: 323-324, 1956.

Ibogaine, an indole alkaloid from Tabernanthe iboga, which has central stimulant properties was measured with the mouse tail flick method alone and in combination with 3 mg/kg morphine for analgesia. Alone, Ibogaine (6 - 24 mg/kg) had no effect but it significantly potentiated morphine analgesia by about 30 to 50%. It also increased LD_{50} dose of morphine and Ibogaine LD_{50} by five fold. It acted in a similar manner on codeine, methadone and ketobemidone. Aminopyrine was not potentiated.

SIGG, E. B., G. CAPRIO and J. A. SCHNEIDER
Synergism of amines and antagonism of reserpine to morphine analgesia. Proc. Soc. Exper. Biol. and Med. 97: 97-100, 1958.

Used tail flick in mice with s. c. doses: 5 mg/kg morphine SO_4 synergized

1. 5-hydroxytryptaime (5-10 mg/kg)
2. tryptamine (100 mg/kg)
3. 5-hydroxytryptophane (30-400 mg/kg)
4. amphetamine (3-5 mg/kg)
5. mescaline (10-50 mg/kg)
6. epinephrine (2-5 mg/kg)

Antagonized by reserpine at 2.5 mg/kg but not by isoreserpine, iproniazid (or iproniazid + reserpine).

Iproniazid, tryptophane or 5-hydroxyindoleacetic acid had no effect. Reserpine antagonism believed to be due to catachol amine depletion, but this has no effect on synergisms. Suggest retardation of demethylation as possible mechanism of synergism.

SLAUGHTER, D. H.
Neostigmine and opiate analgesia. Arch. int. pharmacodyn. 83: 143-148, 1950.

Used Wolff, Hardy and Goodell method on untrained subjects (6) with a double blind. Repeated measurements on same subjects used. Results in units of threshold over 150 min are by integration of difference from control: morphine SO_4 (16 mg), 150; morphine SO_4 (8 mg) + neostigmine methyl SO_4 (0.5 mg), 181; pantophon (20 mg), 91; pantophon (10 mg), 31; pantophon (10 mg) + neostigmine (0.5 mg), 57; dilaudid (6 mg), 327; dilaudid (3 mg),

156; dilaudid (3 mg) + neostigmine (0.5 mg), .223; codeine PO_4 (64 mg), 5; codeine (32 mg), -.7; codeine (32 mg) + neostigmine (0.5 mg), 51; neostigmine alone at 0.5 mg, 81. Neostigmine is said to reduce side effects of the opiates. Drugs were given I.M.

SLAUGHTER, D. H. and D. W. MUNSELL

Some new aspects of morphine action effects on pain. J. Pharmacol. exp. therap. 68: 104-112, 1940.

The investigators used responses of cats having their tail clamped (Eddy method). Drugs given s.c. atropine (.085 mg/kg) and prostigmine (.04 mg/kg) were given alone, in combination with morphine (1.0 mg/kg), and all three together. Prostigmine had no effect of itself but potentiated morphine about 100%. Atropine did not potentiate and reduced the effect of prostigmine potentiation.

SZERB, J. C. and D. H. McCURDY

Concentrations of morphine in blood and brain after intravenous injection of morphine in non-tolerant, tolerant and neostigmine-treated rats. J. Pharmacol. exp. therap. 118: 446-450, 1956.

Determining if neostigmine potentiates by increasing the passage of morphine into the brain by measuring brain morphine with and without neostigmine treatment. Rats were made tolerant by 37.5 mg/kg of morphine per day for seven days, 75.0 mg/kg for the next ten and 150 mg/kg for the last ten. Neostigmine by i.v. 0.2 mg/kg 20 min prior to morphine. Spontaneous activity and blood and brain morphine measured in tolerant and non-tolerant animals. Free morphine of blood and brain of tolerant rats was lower than non-tolerant. Neostigmine did not change the free or bound morphine in blood or brain, but did reduce tolerance to morphine and potentiate its action.

TORDOS, L. and Z. JOBBAGYI

Wirkung von Reserpin auf den Effekt der Analgetika. Acta Physiol. Acad. Sci. Hung. 13: 171-178, 1958.

Using a modified Woolfe-Macdonald method (hot plate) in rats reserpine (0.5 - 1.0 mg/kg) given 60 min prior, potentiated

morphine, pethidine and aminopyrine. Using tail flick method this potentiation was not found.

WIRTH, W.

Versuche zur Kombinierten Wirkung von Megaphen mit stark wirksamen Analgeticis. Arch. f. exp. Path. u. Pharmakol. 222: 75-76, 1954.

Used rats and guinea pigs with a mechanical stimulation method. Found that the addition of chloropromazine reduced threshold doses of morphine, meperidine and dormoran to one half to one third. Lethal dose of opiates was not changed.

WITKIN, L. B., C. F. HEUBNER, F. GALDI, E. O'KEEFE, P. SPITALETTA and A. J. PLUMMER

Pharmacology of 2-amino-indane HCl (SU-8629): A potent non-narcotic analgesic. J. Pharmacol. exp. therap. 133: 400-408, 1961.

Used tail flick method in mice and hot plate method with SU-8629 at 5 mg/kg and morphine at 2 mg/kg. Also used writhing from acetic acid, spontaneous motor activity, blood sugar, EST and gastric motility. Orally, SU-8629 is same potency as morphine but s. c. it is 1/5 as potent. SU-8629 is mild central stimulant similar to amphetamine but 1/4 as potent. SU-8629 not antagonized by nalorphine. Both SU-8629 and amphetamine potentiated morphine analgesia at same dose of 5 mg/kg but amphetamine was more potent.

WITKIN, L. B., M. MAGGIO and W. E. BARRETT

Independence of sedative and analgetic antagonizing effects of two reserpine esters. Proc. Soc. Exper. Biol. and Med. 101: 377-379, 1959.

The experimenters used tail flick in mice and found methylphenidate at 5 mg/kg to potentiate morphine analgesia by about 300%. Reserpine, syrosingopine and methyl-18-0 (dimethylamino benzoyl) reserpate (SU-5171) all antagonized morphine to about the same degree yet all three are not equipotent at sedation.

WITKIN, L. B., M. MAGGIO, E. O'KEEFE and F. GALDI
A study of some central nervous stimulants in mice. Fed. Proc. 19: 269, 1960.

The investigators used tail flick to heat in mice. Morphine analgesia was potentiated by methylphenidate and also by d-amphetamine. Metrazol was found to have no effect and reserpine antagonized analgetic action.

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